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Application No. :	10/806,829	Confirmation No.:	4240
Applicants :	Jian Bai, Steven M. Fischer and J. Michael Flanagan		
Filing Date :	March 22, 2004		
Title :	Ambient Pressure Matrix-Assisted Laser Desorption Ionization (MALDI) Apparatus and Method of Analysis		
Group Art Unit :	81		
Examiner :	Gurzo, Paul M.		
Docket No. :	10980322-4		

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Commissioner for Patents
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RESPONSE TO NOTICE TO COMPLY WITH RULE 37 CFR § 41.202 (a)(1) – (6)

Sir:

This paper responds to the Notice mailed October 6, 2005.

1. 37 CFR § 41.202(a)(1) – Identification of Application and Patent:

This application is U.S. Serial Number 10/806,829, filed March 22, 2004, which is a continuation of U.S. application serial number 09/146,817 filed September 4, 1998, which is a continuation-in-part of U.S. provisional application serial number 60/089,088, filed June 17, 1998, and entitled "Ambient Pressure Matrix-Assisted Laser Desorption Ionization (MALDI) Apparatus and Method of Analysis," naming Jian Bai, Steven M. Fischer and J. Michael Flanagan as inventors.

CERTIFICATE OF MAILING
37 CFR §1.10

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I hereby certify that on the dated listed above, this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service in accordance with 37 C.F.R. § 1.10 as "Express Mail Post Office to Addressee," with sufficient postage in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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The patent is U.S. 6,683,300, filed September 17, 2001, issued January 27, 2004, and assigned to Science & Engineering Services, Inc., Burtonsville, MD (US) and naming Vladimir M. Doroshenko, Victor V. Laiko, Mikhall Yakshin, and Hyo Sang Lee, as inventors.

37 CFR § 41.202(a)(2) – Interfering Claims:

Claims 34–80 of the above-captioned application and at least claims 1-36, 38-56, 49-56, 58-62, 64-77, and 82-85 of the '300 patent recite interfering subject matter.

Proposed Counts: The proposed counts are as follows:

Count I

I. An apparatus for the mass spectroscopic analysis of an analyte solution comprising:

a light source configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;

a mass analyzer configured to mass-analyze said gas-phase ions; and

a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.

Count II

II. An apparatus for the mass spectroscopic analysis of an analyte solution comprising:

a laser configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions at or about atmospheric pressure;

a mass analyzer configured to mass-analyze said gas-phase ions; and

a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.

Count I corresponds to independent Claim 1 of the '300 patent and independent claim 34 of the present application. Count II substantially corresponds to dependent claim 4 of the '300 patent and dependent claim 68 of the instant application, written in independent form to include the claims from which each respectively, depends.

The claims corresponding to Count I recite a basic method and apparatus for desorption and ionization from liquids using an analyte-containing solution.. The claims corresponding to Count II recite desorption and ionization from liquids at atmosphere pressure using an analyte-containing solution.

The following chart identifies the individual claims that correspond to each Count and explains how the claims correspond to each of Counts I and II..

'300 Patent	Count I	10/806,829
Independent claims 1, 28, and 50 recite the same patentable subject as Count I. Dependent claims 2, 3, 6-36, 38-52, 55, 56, 58-62, 64-77, and 82-85 are dependent claims reciting additional limitations on the independent claims but which are not separately patentable from Count I. These dependent claims each recite further characteristics of the basic liquid desorption and ionization system and narrow the independent claims with additional limitations that are not separately patentable from the Count, and correspond to	An apparatus for the mass spectroscopic analysis of an analyte solution, comprising: a light source configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions; a mass analyzer configured to mass-analyze said gas-phase ions; and a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.	Independent claims 34, 51, and 65 recite the same patentable subject matter as Count I. Dependent claims 35, 36, 39-50, 52-64, 66, 67, 70-78, and 80 are dependent claims reciting additional limitations on the independent claims, but which are not separately patentable from Count I. As with the '300 patent claims, these claims recite further limitations on the independent claims and do not constitute separately patentable subject matter. These claims correspond substantially to the exact

the subject matter therein.		language from the '300 patent claims and correspond to the Count in an analogous fashion to the '300 patent claims.
'300 Patent	Count II	10/806,829
Each of dependent claims 4, 5, 53, and 54 recite a method or apparatus necessarily producing gas-phase ions of the analyte at atmospheric pressure. This subject matter corresponds to Count II and is separately patentable from the subject matter of Count I.	An apparatus for the mass spectroscopic analysis of an analyte solution comprising: a laser configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions at or about atmospheric pressure; a mass analyzer configured to mass-analyze said gas-phase ions; and a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.	Each of dependent claims 37, 38, 68, 69, and 79 recite a method or apparatus necessarily producing gas-phase ions of the analyte at atmospheric pressure. This subject matter corresponds to Count II and is separately patentable from the subject matter of Count I.

3. 37 CFR § 41.202(a)(3) – Chart of Claims Corresponding to Count:

The following chart shows how at least one claim of each of the '300 patent and the present application corresponds to each of Count I and Count II.

Claim 28 of '300 Patent	Count I	Claim 65 of 10/806,829
A system for the mass spectroscopic analysis of an analyte solution, comprising:	An apparatus for the mass spectroscopic analysis of an analyte solution, comprising:	An apparatus for the mass spectroscopic analysis of an analyte solution, comprising:
means for irradiating a liquid solution of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;	a light source configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;	a light source configured to irradiate a liquid volume of said analyte solution, without additional matrix added to said analyte solution, to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;
means for mass-analyzing said gas-phase ions; and	a mass analyzer configured to mass-analyze said gas-phase ions; and	a mass analyzer configured to mass-analyze said gas-phase ions; and
means for transferring said gas-phase ions into said means for mass-analyzing.	a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.	means to transfer said gas-phase ions to said mass analyzer.

Claim 53 of '300 Patent	Count II	Claim 68 of 10/806,829
An apparatus for the mass spectroscopic analysis of an analyte solution, comprising:	An apparatus for the mass spectroscopic analysis of an analyte solution comprising:	An apparatus for the mass spectroscopic analysis of an analyte solution, comprising:
a light source configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;	a laser configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a	a light source configured to irradiate a liquid volume of said analyte solution, without additional matrix added to said analyte solution, to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;
a mass analyzer configured to mass-analyze said gas-phase ions; and	surrounding gas to produce gas-phase ions at or about atmospheric pressure;	a mass analyzer configured to mass-analyze said gas-phase ions; and
a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.	a mass analyzer configured to mass-analyze said gas-phase ions; and	means to transfer said gas-phase ions to said mass analyzer.
The apparatus as in claim 50, wherein said gas-phase ions are produced at or about atmospheric pressures.	a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.	The apparatus as in claim 65, wherein said gas-phase ions are produced at or about atmospheric pressures.

The above-identified claims interfere within the meaning of 37 CFR § 41.203(a) because the claims of a party would, if prior art, anticipate or render obvious the subject matter of the claim of the other party and visa versa, as shown herein. In this particular case, the above-

captioned applicants have drafted claim language to substantially correspond to the claims in the issued '300 patent and have fashioned the proposed Counts to closely follow this language. Accordingly, the claims and corresponding Counts recite nearly identical subject matter. With respect to the differences between Count I and Count II proposed above, applicants believe that the content of the application and patent at issue, the pertinent prior art, and the record in the PTO, including a previously-resolved interference referenced below in which a parent of the present application was awarded priority over a competing application, establish that the use of atmospheric pressure conditions for laser desorption and ionization from liquids is separately patentable from the prior art and the content of Count I.

Each independent claim of the '300 patent recites terms substantially as follows: "without an added matrix." This language may be intended to distinguish the claims of the '300 patent from certain prior art, particularly Laiko et al. USP 5,965,884 on the premise that this prior art was interpreted to literally require the presence of an "added matrix" in the analyte solution to achieve desorption and ionization. In fact, this seems to have been the basis for the conclusion of allowable subject matter in the '300 patent based on the Examiner's Statement accompanying the Notice of Allowance.

However, the specification of both the '300 patent and the above-captioned application recognize that desorption and ionization without presence of an "added matrix" is possible in embodiments where the solution of the analyte itself acts as a matrix--specifically because it is capable of absorbing light/laser energy and transferring charge to the analyte. Therefore, the present application describes, and includes within the definition of "matrix," the laser desorption and ionization of analyte ions in a liquid solution based on the inherent ability of the liquid solution to function as the matrix either with or "without an added matrix" as claimed in the '300 patent. In fact, the present application expressly states:

> Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
> * * * *

> The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice. (page 12, line 27 to page 13, line 3).

Thus, applicants submit that the phrase "without an added matrix" is supported by the language in applicants' specification where the liquid solution containing analyte acts as the requisite substance to transfer charge to the analyte whether or not it is treated as "without an added matrix."

4. 37 CFR § 41.202(a)(4) – Explanation Why the Applicants Will Prevail on Priority:

The above-captioned applicants will prevail on priority because:

(1) the present application is a continuation application claiming priority under 35 U.S.C. §120 to U.S. application serial number 09/146,817 filed September 4, 1998. Thus, the applicants enjoy an advantage in constructive reduction to practice of over 3 years.

(2) a parent of the present application was involved in an interference entitled *Jian Bai et al. v. Victor V. Laiko et al.*, Patent Interference No. 104,745, directed to a priority contest to the fundamental technique of atmospheric pressure matrix-assisted laser desorption ionization (AP MALDI) wherein the subject matter of the parent of the present application was deemed entitled to a conception date of 19 December 1997 and an actual reduction to practice of 23 December 1997. Accordingly, the priority advantage held by applicants is even greater than the filing dates would suggest.

(3) An European counterpart of the present application published on December 15, 1999, EPO Application No. 99111331.7, published as EP 0964 427, and is prior art to the '300 patent under 35 U.S.C. §102(b). Accordingly, the '300 patentees cannot establish both priority and validity as to any subject matter contained in the present application and

published in the European counterpart. Therefore, the present applicants must prevail in priority for any patentable invention described in the present specification as against the '300 patent.

(4) One of the co-inventors of the '300 patent, Victor V. Laiko, was a party and member of a different inventive entity in the above-referenced interference and, given the present applicants' priority in that case, it does not appear possible for any subsequent inventive entity of which Mr. Laiko is a member to be entitled to an earlier priority than the present applicants.

(5) 37 CFR § 41.202(a)(5) — Chart Showing Written Description in Applicants' Specification:

The following claims 34-80 were added to the present application by Amendment following filing of the continuation application March 22, 2004. Support for these claims exists in the present specification as indicated in the following chart.

Claims of 10/806,829	Support in specification
34. A method for mass spectroscopic analysis of an analyte solution, comprising: irradiating a liquid volume of said analyte solution, without additional matrix added to said analyte solution, matrix with a light beam to desorb solution-specific ions into a surrounding gas to produce gas-phase ions; transferring said gas-phase ions to a mass analyzer; and mass-analyzing said gas-phase ions by said mass analyzer.	In another embodiment the present invention relates to a method for analyzing a sample that may contain at least one analyte comprising: (a) providing a matrix containing the sample; (b) maintaining the sample matrix in a condition of ambient pressure greater than 13.3 Pa (100 mTorr) while directing laser energy onto the matrix to desorb and ionize at least a portion of the at least one analyte; (c) directing at least a portion of the ionized at least one analyte into a mass analysis device, and (d) mass analyzing the portion of the at least one analyte that is received by the mass analysis device. (page 8, lines 11-20) Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5) The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice. (page 12, line 27 to page 13, line 3).

35. The method as in claim 34, wherein the step of irradiating with a light beam comprises: irradiating with a laser beam.	Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)
36. The method as in claim 35, wherein the step of irradiating with a laser beam comprises: pulsing with a laser beam.	By contrast, MALDI is a pulsed technique wherein ionization of the analyte occurs via a transfer of charge (often a proton) between the absorbing matrix which is irradiated by a pulsed laser of the proper wavelength. (page 3, lines 18-20)
37. The method as in claim 36, wherein the step of irradiating comprises: producing said gas-phase ions at or about atmospheric pressures.	Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred. In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
38. The method as in claim 34, wherein the step of transferring comprises: transferring said gas-phase ions to an inlet port of a mass spectrometer equipped with an atmospheric pressure interface.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)

39. The method as in claim 34, further comprising: depositing said analyte solution on a surface, prior to the step of irradiating.	The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
40. The method as in claim 39, wherein the step of depositing comprises: depositing a matrix-free analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge to or from the analyte. (page 11, lines 1-5) The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
41. The method as in claim 38, wherein said step of depositing comprises: depositing said analyte solution on at least one of metal surface, and a membrane.	Suitable surfaces for depositing the matrix/analyte mixture include a probe tip, sample stage and the like. The probe tip or sample stage may be constructed from a number of materials including metals (such as stainless steel, gold, silver, aluminum, and the like), semiconductors (e.g. silicon), and insulators (such as quartz, glass or polymers, e.g. PDVF (or PU defined below)). (page 12, lines 1-5) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or

	combinations thereof. (page 10, lines 28-31)
42. The method as in claim 34, wherein said analyte solution is in an electrophoresis gel.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
43. The method as in claim 39, wherein said step of depositing comprises: depositing said analyte solution on a flat surface.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)

44. The method as in claim 39, wherein said step of depositing comprises: depositing samples of multiple analyte solutions on an array.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
45. The method as in claim 34, wherein said step of transferring comprises: placing said analyte solution close to at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)

46. The method as in claim 34, wherein said step of transferring comprises: generating an electric field between said analyte solution and at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port to assist in transfer of said gas-phase ions into the mass analyzer.	The potential gradient may be produced by holding the probe tip or sample stage at ground potential and applying a high voltage to the passageway; by applying a high voltage to the probe tip or sample stage and holding the passageway at ground potential; or any other arrangement which would establish a potential gradient between the entrance to the passage-way and the probe tip or sample stage and cause the ions produced to be drawn toward the passageway entrance. (page 12, lines 18-23)
47. The method as in claim 34, wherein said step of transferring comprises: producing a gas flow to transfer said gas-phase ions toward at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port.	A gas which is introduced to the ionization enclosure which entrains and carries the ionized analytes into the passageway. (page 11, lines 14-15)
48. The method as in claim 34, wherein said step of mass-analyzing comprises: analyzing liquid solutions of organic and inorganic compounds including peptides, proteins, nucleic acids, polymers and other compounds of biological significance.	Of particular interest are biomolecules and fragments thereof including but not limited to biopolymers such as DNA, RNA, lipids, peptides, protein, carbohydrates – natural and synthetic organisms and fragments thereof such as bacteria, algae, fungi, viral particles, plasmids, cells and the like. (page 6, lines 24-27) For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. (page 11, lines 5-8)

49. The method as in claim 34, wherein said step of irradiating comprises: irradiating said analyte solution at a wavelength which is absorbed by said analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
50. The method as in claim 39, further comprising: providing a liquid flow of said analyte solution to said surface.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
51. A system for the mass spectroscopic analysis of an analyte solution, comprising: means for irradiating a liquid volume of said analyte solution, without additional matrix added to said analyte solution, to desorb solution-specific ions into a surrounding gas to produce gas-phase ions; means for mass-analyzing said gas-phase ions; and means for transferring said gas-phase ions into said means for mass-analyzing.	In one embodiment, the present invention relates to an apparatus for ionizing at least one analyte in a sample for delivery to a mass analysis device, comprising: (a) an ionization enclosure including a passageway configured for delivery of ions to the mass analysis device; (b) means to maintain the ionization enclosure at an ambient pressure of greater than 100 mTorr; (c) a holder configured for maintaining a matrix containing the sample in the ionization enclosure at said ambient pressure; (d) a source of laser energy including means associated with the ionization enclosure for directing the laser energy onto said matrix maintained by the holder at the ambient pressure to desorb and ionize at least a portion of the analyte in the sample, and (e) means for directing at least a portion of the at least one ionized analyte into the passageway. (page 7, lines 4-16) The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector

	may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
52. The system as in claim 51, further comprising: means for depositing said analyte solution on a surface.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
53. The system as in claim 52, wherein said means for depositing is configured to deposit a matrix-free analyte solution.	"Holder" also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the like. (page 10, lines 25-27)
54. The system as in claim 52, wherein said surface comprises: at least one of a metal surface and a membrane.	Suitable surfaces for depositing the matrix/analyte mixture include a probe tip, sample stage and the like. The probe tip or sample stage may be constructed from a number of materials including metals (such as stainless steel, gold, silver, aluminum, and the like), semiconductors (e.g. silicon), and insulators (such as quartz, glass or polymers, e.g. PDVF (or PU defined below)). (page 12,

	lines 1-5) "Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
55. The system as in claim 52, wherein said surface comprises an electrophoresis gel.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, line 22-25)
56. The system as in claim 52, wherein said surface comprises an array of multiple analyte solutions.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
57. The system as in claim 51, wherein said means for transferring comprises: an electric field between said analyte solution and an inlet of said means for mass analyzing to assist in transfer of said gas-phase ions into the means for mass analyzing.	The potential gradient may be produced by holding the probe tip or sample stage at ground potential and applying a high voltage to the passageway; by applying a high voltage to the probe tip or sample stage and holding the passageway at ground potential; or any other arrangement which would establish a potential gradient between the entrance to the passage-way and the probe tip or sample stage and cause the ions produced to be drawn toward the passageway entrance. (page 12, lines 18-23)
58. The system as in claim 51, wherein said means for irradiating a surface comprises: means for irradiating at a wavelength which is absorbed by said analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)

59. The system as in claim 51, wherein said means for irradiating comprises: means for pulsing an infrared laser light.	By contrast, MALDI is a pulsed technique wherein ionization of the analyte occurs via a transfer of charge (often a proton) between the absorbing matrix which is irradiated by a pulsed laser of the proper wavelength. (page 3, lines 18-20)
60. The system as in claim 52, further comprising: means for providing a liquid flow of said analyte solution to said surface.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
61. The system as in claim 54, wherein said means for providing comprises: means for moving said surface.	In one application, the laser is stationary and the at least one sample are multiple samples and the multiple samples are positioned and sequentially analyzed in an organized or a random manner. (page 13, lines 27-29) Sample holder (14) may be a multi-well sample plate, which is moved in an organized manner by a conventional multi-axis (XYZ) sample translation and rotation stage (15). This stage is programmable and can operate under data system control. (page 15, lines 27-29)
62. The system as in claim 54, wherein said means of providing comprises: means for moving said surface relative to said means for mass analyzing.	In one application, the laser is stationary and the at least one sample are multiple samples and the multiple samples are positioned and sequentially analyzed in an organized or a random manner. (page 13, lines 27-29) Sample holder (14) may be a multi-well sample plate, which is moved in an organized manner by a conventional multi-axis (XYZ) sample translation and rotation stage (15). This stage is programmable and can operate under data system control. (page 15, lines 27-29)
63. The system as in claim 54, wherein said means for providing comprises:	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page

means for providing a continuous flow of the analyte solution.	13, lines 8-10)
64. The system as in claim 51, wherein said means for transferring comprises: an enclosure with a gas under defined pressure and temperature conditions.	Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred. In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
65. An apparatus for the mass spectroscopic analysis of an analyte solution, comprising: a light source configured to irradiate a liquid volume of said analyte solution, without additional matrix added to said analyte solution, to desorb solution-specific ions into a surrounding gas to produce gas-phase ions; a mass analyzer configured to mass-analyze said gas-phase ions; and means to transfer said gas-phase ions to said mass analyzer.	In one embodiment, the present invention relates to an apparatus for ionizing at least one analyte in a sample for delivery to a mass analysis device, comprising: (a) an ionization enclosure including a passageway configured for delivery of ions to the mass analysis device; (b) means to maintain the ionization enclosure at an ambient pressure of greater than 100 mTorr; (c) a holder configured for maintaining a matrix containing the sample in the ionization enclosure at said ambient pressure; (d) a source of laser energy including means associated with the ionization enclosure for directing the laser energy onto said matrix maintained by the holder at the ambient pressure to desorb and ionize at least a portion of the analyte in the sample, and (e) means for directing at least a portion of the at least one ionized analyte into the passageway. (page 7, lines 4-16)

	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
66. The apparatus as in claim 65, wherein the light source comprises a laser beam.	Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)
67. The apparatus as in claim 66, wherein the laser beam is configured to generate a pulsed laser beam.	By contrast, MALDI is a pulsed technique wherein ionization of the analyte occurs via a transfer of charge (often a proton) between the absorbing matrix which is irradiated by a pulsed laser of the proper wavelength. (page 3, lines 18-20)
68. The apparatus as in claim 65, wherein said gas-phase ions are produced at or about atmospheric pressures.	Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred. In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
69. The apparatus as in claim 65, wherein the transfer mechanism includes an inlet port on a mass spectrometer equipped	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this

with an atmospheric pressure interface.	application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
70. The apparatus as in claim 65, further comprising: a substrate configured to receive said analyte solution.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
71. The apparatus as in claim 70, wherein said surface comprises: at least one of a metal surface and a membrane.	Suitable surfaces for depositing the matrix/analyte mixture include a probe tip, sample stage and the like. The probe tip or sample stage may be constructed from a number of materials including metals (such as stainless steel, gold, silver, aluminum, and the like), semiconductors (e.g. silicon), and insulators (such as quartz, glass or polymers, e.g. PDVF (or PU defined below)). (page 12, lines 1-5) "Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or

	combinations thereof. (page 10, lines 22-25)
72. The apparatus as in claim 70, wherein said surface comprises an electrophoresis gel.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
73. The apparatus as in claim 70, wherein said surface comprises: an array with multiple analyte solutions.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
74. The apparatus as in claim 65, wherein said mass analyzer comprises: at least one of an inlet orifice attached to an inlet port of a mass spectrometer and a capillary tube attached to said inlet port.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detetor may be an ion sampling orifice, capillary of the like. (page 12, lines 11-13) The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s) or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
75. The apparatus as in claim 65, wherein the transfer means comprises: an electric field between said analyte solution and at least one of an inlet port and a capillary tube attached to said inlet port.	The potential gradient may be produced by holding the probe tip or sample stage at ground potential and applying a high voltage to the passageway; by applying a high voltage to the probe tip or sample stage and holding the passageway at ground potential; or any other arrangement which would establish a potential gradient between the entrance to the passage-way and the probe tip or sample stage and cause the ions produced to be drawn toward the passageway entrance. (page 12, lines 18-23)
76. The apparatus as in claim 65,	Of particular interest are biomolecules and

wherein the analyte solution comprises: a liquid solution including at least one of peptides, proteins, nucleic acids, polymers and other compounds of biological industrial significance.	fragments thereof including but not limited to biopolymers such as DNA, RNA, lipids, peptides, protein, carbohydrates – natural and synthetic organisms and fragments thereof such as bacteria, algae, fungi, viral particles, plasmids, cells and the like. (page 6, lines 24-27) For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. (page 11, lines 5-8)
77. The apparatus as in claim 65, wherein said light source is configured to irradiate said analyte solution with laser pulses at a wavelength which is absorbed by the analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
78. The apparatus as in claim 65, further comprising a high-performance liquid chromatograph or a CE.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
79. The apparatus as in claim 65, further comprising: an enclosure filled with a gas under atmospheric pressure.	(a) an ion source having an ionization enclosure and a mass analysis device having a mass analysis enclosure, the ionization enclosure being connected with the mass analysis enclosure through a passageway configured for delivery of ions from the ion source to the mass analysis device. (page 7, lines 19-22) "Means for maintaining ambient (or atmospheric) pressure" refers to methods and equipment which are currently available. These include but are not limited to . . . (2) gas

	which is introduced to the ionization enclosure to produce above ambient pressure and optionally above atmospheric pressure. (page 11, line _____)
80. The apparatus as in claim 65, wherein said analyte solution comprises: a matrix-free analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5) The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)

(6) 37 CFR § 41.202(a)(6) — Disclosure Supporting Constructive Reduction to Practice Within Scope of Interfering Subject Matter:

Applicants wish to be accorded benefit of a constructive reduction to practice based on the disclosure of the present specification for each claim of the present application that is within the scope of the interfering subject matter, and specifically for each claim of the present application that corresponds to either Count I or Count II. The disclosure in the present specification is set forth in subsection (5) above, which is specifically incorporated by reference herein.

Applicants also wish to be accorded benefit of a constructive reduction to practice based on the disclosure of the present specification that supports the claims of the '300 patent that are within the scope of the interfering subject matter.

The constructive reduction to practice to which applicants should be accorded benefit is shown in the following chart for each claim of the '300 patent deemed to correspond to either Count I or Count II.

'300 Patent Claims	10/806,829 Specification
1. A method for mass spectroscopic analysis of an analyte solution, comprising: irradiating a liquid volume of said analyte solution without an added matrix with a light beam to desorb solution-specific ions into a surrounding gas to produce gas-phase ions; transferring said gas-phase ions to a mass analyzer; and mass-analyzing said gas-phase ions by said mass analyzer.	In another embodiment the present invention relates to a method for analyzing a sample that may contain at least one analyte comprising: (a) providing a matrix containing the sample; (b) maintaining the sample matrix in a condition of ambient pressure greater than 13.3 Pa (100 mTorr) while directing laser energy onto the matrix to desorb and ionize at least a portion of the at least one analyte; (c) directing at least a portion of the ionized at least one analyte into a mass analysis device, and (d) mass analyzing the portion of the at least one analyte that is received by the mass analysis device. (page 8, lines 11-20) Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5) The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice. (page12, line 27 to page 13, line 3) The sampling may occur using a static or a flowing liquid sample, such as the effluent from

	an HPLC, CE, or syringe pump. (page 13, lines 8-10)
2. The method as in claim 1, wherein the step of irradiating with a light beam comprises: irradiating with a laser beam.	Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)
3. The method as in claim 2, wherein the step of irradiating with a laser beam comprises: pulsing with a laser beam.	By contrast, MALDI is a pulsed technique wherein ionization of the analyte occurs via a transfer of charge (often a proton) between the absorbing matrix which is irradiated by a pulsed laser of the proper wavelength. (page 3, lines 18-20)
4. The method as in claim 3, wherein the step of irradiating comprises: producing said gas-phase ions at or about atmospheric pressures.	Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred. In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
5. The method as in claim 1, wherein the step transferring comprises: transferring said gas-phase ions to an inlet port of a mass spectrometer equipped with an atmospheric pressure interface.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)

6. The method as in claim 1, further comprising: depositing said analyte solution on a substrate, prior to the step of irradiating, to produce at least one of a droplet and a thin liquid layer.	The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
7. The method as in claim 6, wherein the step of depositing comprises: depositing a matrix-free analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5) The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
8. The method as in claim 6, wherein the step of depositing comprises: producing said droplet with said liquid volume less than 2 .mμl.	Figures 6A and 6B show ambient pressure MALDI data of a tryptic digest of bovine cytochrome c (14 pmoles deposited on a sample stage). (page 17, lines 12-13)
9. The method as in claim 6, wherein said step of depositing comprises: depositing said analyte solution on at least one of a gold surface, a stainless steel surface, a substrate including at least one well, and a substrate including at least one groove.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. "Holder" also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the like. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix

	is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) Suitable surfaces for depositing the matrix/analyte mixture include a probe tip, sample stage and the like. The probe tip or sample stage may be constructed from a number of materials including metals (such as stainless steel, gold, silver, aluminum, and the like), semiconductors (e.g. silicon), and insulators (such as quartz, glass or polymers, e.g. PDVF (or PU defined below)). (page 12, lines 1-5)
10. The method as in claim 6, wherein said step of depositing comprises: depositing said analyte solution on at least one of a frit and a gel.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
11. The method as in claim 10, wherein said gel is formed by a biopolymer separation using a two-dimensional gel electrophoresis method.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
12. The method as in claim 6, wherein said step of depositing comprises: depositing said analyte solution on a surface of the substrate, said surface configured to flatten an exposed surface of said analyte solution.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip

	array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
13. The method as in claim 12, wherein said step of depositing said analyte solution on a surface comprises: depositing said analyte solution on a curved exposed surface.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
14. The method as in claim 6, wherein said step of depositing comprises: depositing samples of multiple analyte solutions on an array of positions on the substrate.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)

15. The method as in claim 1, wherein said step of transferring comprises: placing said analyte solution close to at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
16. The method as in claim 1, wherein said step of transferring comprises: generating an electric field between said analyte solution and at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port to assist in transfer of said gas-phase ions into the mass analyzer.	The potential gradient may be produced by holding the probe tip or sample stage at ground potential and applying a high voltage to the passageway; by applying a high voltage to the probe tip or sample stage and holding the passageway at ground potential; or any other arrangement which would establish a potential gradient between the entrance to the passage-way and the probe tip or sample stage and cause the ions produced to be drawn toward the passageway entrance. (page 12, lines 18-23)
17. The method as in claim 1, wherein said step of transferring comprises: producing a gas flow with at least one gas nozzle, said gas flow being configured to transfer said gas-phase ions toward at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port.	A gas which is introduced to the ionization enclosure which entrains and carries the ionized analytes into the passageway. (page 11, lines 14-15)
18. The method as in claim 1, wherein said step of irradiating comprises: irradiating a liquid solution including at least one of water, organic fluid, inorganic fluid, and a mixture thereof.	The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the

	like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice. (page 12, line 27 to page 13, line 3)
19. The method as in claim 1, wherein said step of mass-analyzing comprises: analyzing liquid solutions of organic and inorganic compounds including peptides, proteins, nucleic acids, polymers, drugs and other compounds of biological, medical, or industrial significance.	Of particular interest are biomolecules and fragments thereof including but not limited to biopolymers such as DNA, RNA, lipids, peptides, protein, carbohydrates – natural and synthetic organisms and fragments thereof such as bacteria, algae, fungi, viral particles, plasmids, cells and the like. (page 6, lines 24-27) For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. (page 11, lines 5-8)
20. The method as in claim 1, wherein said step of irradiating comprises: irradiating said analyte solution at a wavelength which is absorbed by said analyte solution within a few wavelengths of the light beam.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
21. The method as in claim 1, wherein said step of irradiating comprises: irradiating an hydrous solution with infrared laser pulses at a wavelength close to 3 .mμm.	The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid

	such as ice. (page 12, line 27 to page 13, line 3) For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. (page 11, lines 5-8) Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)
22. The method as in claim 6, further comprising: providing a liquid flow of said analyte solution to said substrate through a capillary transfer line to compensate for analyte solution losses due to laser pulse irradiation and evaporation.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
23. The method as in claim 22, wherein said step of providing comprises: moving said substrate with respect to the capillary transfer line; and supplying the liquid flow of said analyte solution to the substrate to maintain a deposit of a thin liquid layer to thereby increase ionization efficiency.	"Flowing" refers to a liquid sample or matrix which is moving and from which the sample and matrix is analyzed. (page 10, lines 20-21) "Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix

	is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
24. The method as in claim 22, wherein said step of providing comprises: moving said substrate with respect to an inlet port of said mass analyzer; and supplying the liquid flow of said analyte solution to the substrate to maintain a deposit of a thin liquid layer to thereby increase ionization efficiency.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
25. The method as in claim 22, wherein said step of providing comprises: sensing a balance of said analyte solution; and regulating the balance by adjusting at least one of said liquid flow, a laser pulse energy, and a laser repetition rate.	In figure 4G the laser firing are designated as 41, 42, 43 and 44 related to the (M+H)+ of bradykinin. (page 17, lines 10-11)
26. The method as in claim 25, wherein said step of providing comprises: providing a continuous flow of the analyte solution.	"Flowing" refers to a liquid sample or matrix which is moving and from which the sample and matrix is analyzed. (page 10, lines 20-21) "Holder" also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the

	like. (page 10, lines 25-27)
27. The method as in claim 25, wherein said step of providing comprises: on-line coupling of said liquid flow to the mass analyzer.	"Holder" also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the like. (page 10, lines 25-27)
28. A system for the mass spectroscopic analysis of an analyte solution, comprising: means for irradiating a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions into a surrounding gas to produce gas-phase ions; means for mass-analyzing said gas-phase ions; and means for transferring said gas-phase ions into said means for mass-analyzing.	In one embodiment, the present invention relates to an apparatus for ionizing at least one analyte in a sample for delivery to a mass analysis device, comprising: (a) an ionization enclosure including a passageway configured for delivery of ions to the mass analysis device; (b) means to maintain the ionization enclosure at an ambient pressure of greater than 100 mTorr; (c) a holder configured for maintaining a matrix containing the sample in the ionization enclosure at said ambient pressure; (d) a source of laser energy including means associated with the ionization enclosure for directing the laser energy onto said matrix maintained by the holder at the ambient pressure to desorb and ionize at least a portion of the analyte in the sample, and (e) means for directing at least a portion of the at least one ionized analyte into the passageway. (page 7, lines 4-16)
29. The system as in claim 28, further comprising: means for depositing said analyte solution on a surface of a substrate.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an

	electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
30. The system as in claim 29, wherein said means for depositing is configured to deposit a matrix-free analyte solution.	"Holder" also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the like. (page 10, lines 25-27)
31. The system as in claim 29, wherein said substrate comprises: at least one of a substrate including at least one of a gold surface, a stainless steel surface, at least one well, and at least one groove.	Suitable surfaces for depositing the matrix/analyte mixture include a probe tip, sample stage and the like. The probe tip or sample stage may be constructed from a number of materials including metals (such as stainless steel, gold, silver, aluminum, and the like), semiconductors (e.g. silicon), and insulators (such as quartz, glass or polymers, e.g. PDVF (or PU defined below)). (page 12, lines 1-5)
32. The system as in claim 29, wherein said substrate comprises: at least one of a frit and a gel.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)

33. The system as in claim 29, wherein means for depositing comprises: means for forming at least one of a droplet and a thin layer of said analyte solution.	The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
34. The system as in claim 33, wherein said droplet comprises a droplet with said liquid volume less than 2 .mu.l.	Figures 6A and 6B show ambient pressure MALDI data of a tryptic digest of bovine cytochrome c (14 pmoles deposited on a sample stage). (page 9, lines 24-25)
35. The system as in claim 29, wherein said substrate comprises: an array with positions on the array configured to deposit samples of multiple analyte solutions.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
36. The system as in claim 29, wherein said means for depositing comprises: means for flattening an exposed surface of said analyte solution.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional

	single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
38. The system as in claim 28, wherein said means for transferring comprises: an electric field between said analyte solution and an inlet of said means for mass analyzing to assist in transfer of said gas-phase ions into the means for mass analyzing.	The potential gradient may be produced by holding the probe tip or sample stage at ground potential and applying a high voltage to the passageway; by applying a high voltage to the probe tip or sample stage and holding the passageway at ground potential; or any other arrangement which would establish a potential gradient between the entrance to the passage-way and the probe tip or sample stage and cause the ions produced to be drawn toward the passageway entrance. (page 12, lines 18-23)
39. The system as in claim 28, wherein said means for transferring comprises: at least one gas nozzle configured to produce a gas flow to transfer said gas-phase ions toward an inlet of said means for mass analyzing.	A gas which is introduced to the ionization enclosure which entrains and carries the ionized analytes into the passageway. (page 11, lines 14-15)
40. The system as in claim 28, wherein said means for irradiating a surface comprises: means for irradiating at a wavelength which is absorbed by said analyte solution within a few wavelengths of light from said means for irradiating.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
41. The system as in claim 28, wherein said means for irradiating comprises: means for pulsing an infrared laser light at a wavelength of about 3 .mu.m.	Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)

42. The system as in claim 29, further comprising: means for providing a liquid flow of said analyte solution to said substrate to compensate for analyte solution losses due to irradiation and evaporation.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
43. The system as in claim 42, wherein said means for providing comprises: means for moving said substrate relative to said means for providing; and means for supplying said liquid flow to the substrate to maintain a deposit of a thin liquid layer.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
44. The system as in claim 42, wherein said means of providing comprises: means for moving said substrate relative to said means for mass analyzing; and means for supplying the liquid flow of said analyte solution to the substrate to maintain a deposit of a thin liquid layer to thereby increase ionization efficiency.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
45. The system as in claim 42, wherein said means for providing comprises: means for sensing a balance of said analyte solution; and means for regulating said balance by adjusting to at least one of said liquid flow, a laser pulse energy, and a laser repetition rate.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
46. The system as in claim 42, wherein said means for providing comprises: means for providing a continuous flow of the analyte solution.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)

47. The system as in claim 42, wherein said means for providing comprises: means for on-line coupling of said means for providing to said means for mass analyzing.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
48. The system as in claim 42, wherein said means for providing comprises: means for directing a part of an effluent solution from said means for providing into said means for mass analyzing.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
49. The system as in claim 28, wherein said means for transferring comprises: a housing filled with a gas under defined pressure and temperature conditions.	(a) an ion source having an ionization enclosure and a mass analysis device having a mass analysis enclosure, the ionization enclosure being connected with the mass analysis enclosure through a passageway configured for delivery of ions from the ion source to the mass analysis device, the ion source including (page 7, lines 19-22) Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred. In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
50. An apparatus for the mass spectroscopic analysis of an analyte solution, comprising: a light source configured to irradiate a liquid volume of said analyte solution without an added matrix to desorb solution-specific ions	In one embodiment, the present invention relates to an apparatus for ionizing at least one analyte in a sample for delivery to a mass analysis device, comprising: a source of laser energy including means

into a surrounding gas to produce gas-phase ions; a mass analyzer configured to mass-analyze said gas-phase ions; and a transfer mechanism configured to transfer said gas-phase ions to said mass analyzer.	associated with the ionization enclosure for directing the laser energy onto said matrix maintained by the holder at the ambient pressure to desorb and ionize at least a portion of the analyte in the sample, and (page 7, lines 12-14) The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
51. The apparatus as in claim 50, wherein the light source comprises a laser beam.	Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)
52. The apparatus as in claim 51, wherein the laser beam is configured to generate a pulsed laser beam.	By contrast, MALDI is a pulsed technique wherein ionization of the analyte occurs via a transfer of charge (often a proton) between the absorbing matrix which is irradiated by a pulsed laser of the proper wavelength. (page 3, lines 18-20)
53. The apparatus as in claim 50, wherein said gas-phase ions are produced at or about atmospheric pressures.	Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred.

	In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
54. The apparatus as in claim 50, wherein the transfer mechanism includes an inlet port on a mass spectrometer equipped with an atmospheric pressure interface.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s), lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, lines 11-17)
55. The apparatus as in claim 50, further comprising: a substrate configured to receive said analyte solution.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
56. The apparatus as in claim 55, wherein said substrate comprises: at least one of a gold surface, a stainless steel surface, at least one well, and at least one groove.	Suitable surfaces for depositing the matrix/analyte mixture include a probe tip, sample stage and the like. The probe tip or sample stage may be constructed from a number of materials including metals (such as stainless steel, gold, silver, aluminum, and the like), semiconductors (e.g. silicon), and insulators (such as quartz, glass or polymers, e.g. PDVF (or PU defined below)). (page 12, lines 1-5)
58. The apparatus as in claim 55, wherein said substrate includes at least one of a frit and a gel.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation

	wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
59. The apparatus as in claim 58, wherein said gel comprises: a gel formed by a biopolymer separation using a two-dimensional gel electrophoresis method.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25) "Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31)
60. The apparatus as in claim 55, wherein said substrate comprises: a surface configured to flatten a surface of said analyte solution.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article.

	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
61. The apparatus as in claim 60, wherein said surface comprises: a curved exposed surface.	"Location of sample" refers to the situation wherein the said at least one analyte in a matrix is located on a surface; on or in one or more wells of a multi-well microtitre plate; microchip away; on or from a thin layer chromatographic plate on, in or from an electrophoresis gel; on or from a membrane, or combinations thereof. (page 10, lines 28-31) The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)
62. The apparatus as in claim 55, wherein said substrate comprises: an array with positions on the array configured to deposit multiple analyte solutions.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
64. The apparatus as in claim 50, wherein said mass analyzer comprises: at least one of an inlet orifice attached to an inlet port of a mass spectrometer and a capillary tube attached to said inlet port.	The passageway from the AP-MALDI source to the ion optics and mass analyzer/detector may be an ion sampling orifice, capillary or the like. The term "passageway" as used in this application, means "ion transport guide" in any form whatever. It is possible that the passageway be of such short length relative to the opening diameter that it may be called an orifice. Other ion transport guides including capillary(s), multiple ion guide(s), skimmer(s),

	lense(s), or combinations thereof which are or may come to be used can operate successfully in this invention. (page 12, line 11-17)
65. The apparatus as in claim 50, wherein the transfer mechanism comprises: an electric field between said analyte solution and at least one of an inlet port and a capillary tube attached to said inlet port.	The potential gradient may be produced by holding the probe tip or sample stage at ground potential and applying a high voltage to the passageway; by applying a high voltage to the probe tip or sample stage and holding the passageway at ground potential; or any other arrangement which would establish a potential gradient between the entrance to the passage-way and the probe tip or sample stage and cause the ions produced to be drawn toward the passageway entrance. (page 12, lines 18-23)
66. The apparatus as in claim 50, further comprising: at least one gas nozzle configured to transfer said gas-phase ions toward at least of an inlet orifice attached to an inlet port of a mass spectrometer and a capillary tube attached to said inlet port.	A gas which is introduced to the ionization enclosure which entrains and carries the ionized analytes into the passageway. (page 11, lines 14-15)
67. The apparatus as in claim 50, wherein the analyte solution comprises: a liquid solution including at least one of water, organic fluids, inorganic fluids, and a mixture thereof.	The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice. (page 12, line 27 to page 13, line 3)

68. The apparatus as in claim 50, wherein the analyte solution comprises: a liquid solution including at least one of peptides, proteins, nucleic acids, polymers, drugs, and other compounds of biological, medical, or industrial significance.	Of particular interest are biomolecules and fragments thereof including but not limited to biopolymers such as DNA, RNA, lipids, peptides, protein, carbohydrates – natural and synthetic organisms and fragments thereof such as bacteria, algae, fungi, viral particles, plasmids, cells and the like. (page 6, lines 24-27) For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. (page 11, lines 5-8)
69. The apparatus as in claim 50, wherein said light source is configured to irradiate said analyte solution with laser pulses at a wavelength which is absorbed by the analyte solution within a few wavelengths of light from the light source.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
70. The apparatus as in claim 50, wherein said light source is configured to irradiate said analyte solution at a wavelength which is absorbed by the analyte solution within a few wavelengths of light from the light source.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5)
71. The apparatus as in claim 50, wherein the analyte solution comprises a hydrous solution and the hydrous solution is irradiated by infrared laser pulses at a wavelength close to 3 .mu.m.	The matrix, which may be composed of any small molecules which absorb energy at the wavelength of the laser, is capable of transferring charge to the analyte following absorption. Suitable matrix materials include cinnamic acid derivatives (such as α-cyano-4-hydroxycinnamic acid and sinapinic acid), dihydroxybenzoic acid derivatives (such as 2.5-dihydroxybenzoic acid), nicotinic acid, sugars, glycerol, water and the like. Suitable solvents include methanol, acetonitrile, water and the

	like. The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice. (page 12, line 27 to page 13, line 3) For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. (page 11, lines 5-8) Suitable lasers include UV, VIS, and IR lasers such as nitrogen lasers, CO_2 lasers, Er-YAG lasers, Nd-YAG, Er-YILF, Er-YSGG and the like. Typical laser energies which are useful in AP-MALDI analysis of biopolymers are 10^6-10^9 watts/cm^2. Typical laser wavelengths are 200-600 nm (UV-VIS wavelengths) and 1.4-12 μm (IR wavelengths), preferably 1.4-4 μm. (page 12, lines 6-10)
72. The apparatus as in claim 55, further comprising: a supply mechanism configured to supply the analyte solution to said substrate.	The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
73. The apparatus as in claim 72, wherein the supply mechanism comprises: a capillary transfer line.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10) "Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or

	more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
74. The apparatus as in claim 73, further comprising: a motion mechanism configured to move said substrate with respect to the capillary transfer line; and a supply mechanism configured to supply the analyte solution to the substrate to maintain a thin liquid layer to thereby increase ionization efficiency.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10) "Flowing" refers to a liquid sample or matrix which is moving and from which the sample and matrix is analyzed. (page 10, lines 20-21) "Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
75. An apparatus as in claim 74, wherein the supply mechanism includes a frit at an exit end of said supply mechanism to interface the liquid flow of the analyte solution with light from said light source.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
76. The apparatus as in claim 55, further comprising: a motion mechanism configured to move said substrate with respect to an inlet port of said mass analyzer; and a supply mechanism configured to supply a liquid flow of the analyte solution to the substrate to maintain a thin liquid layer to thereby increase ionization efficiency.	In one application, the laser is stationary and the at least one sample are multiple samples and the multiple samples are positioned and sequentially analyzed in an organized or a random manner. (page 13, lines 27-29_ Sample holder (14) may be a multi-well sample plate, which is moved in an organized manner by a conventional multi-axis (XYZ) sample translation and rotation stage (15). This stage is programmable and can operate under data system control. (page 15, lines 27-29)

	"Flowing" refers to a liquid sample or matrix which is moving and from which the sample and matrix is analyzed. (page 10, lines 20-21) "Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
77. An apparatus as in claim 76, wherein the supply mechanism includes a frit at an exit end of said supply mechanism to interface the liquid flow of the analyte solution with light from said light source.	"Holder" refers to a holder for a sample and matrix in this art. Holder includes, but is not limited to, location on a surface; on or in one or more wells of a multi-well microtitre plate; on a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from a membrane, or combinations thereof. (page 10, lines 22-25)
79. The apparatus as in claim 78, further comprising: a liquid separation apparatus configured to provide a continuous flow of the analyte solution to the mass analyzer to thereby provide on-line coupling to said mass analyzer.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
80. The apparatus as in claim 79, wherein the liquid separation apparatus includes at least one of a high-performance liquid chromatograph and a capillary zone electrophoresis unit.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)
81. The apparatus as in claim 79, further comprising: a flow splitter configured to direct a part of an effluent solution from said liquid separation apparatus into said mass analyzer.	The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)

82. The apparatus as in claim 50, further comprising: a housing filled with a gas under defined pressure and temperature conditions.	an ion source having an ionization enclosure and a mass analysis device having a mass analysis enclosure, the ionization enclosure being connected with the mass analysis enclosure through a passageway configured for delivery of ions from the ion source to the mass analysis device, the ion source including: (page 7, lines 19-22) Atmospheric pressure is a subset of ambient pressure and refers to the normal air pressure, e.g. 760 mm Hg at sea level. Near or about atmospheric pressure refers to pressures that are between about +15% and -15% of atmospheric pressure, preferably between about +10% and -10% more preferably between about +5% and -5%. Atmospheric pressure is most preferred. In some cases, a positive pressure (e.g. inert gas) is on the system to control the flow. (page 10, lines 13-18)
83. The apparatus as in claim 50, wherein said liquid volume comprises: a volume of a droplet less than 2 .mu.l.	Figures 6A and 6B show ambient pressure MALDI data of a tryptic digest of bovine cytochrome c (14 pmoles deposited on a sample stage). (page 9, lines 24-25)
84. The apparatus as in claim 50, wherein said liquid volume comprises: a volume of a thin liquid layer atop a substrate.	The analyte in a matrix in one embodiment is located on a surface; on or in one or more wells of a multi-well microtitre plate or a microchip array; on or from a thin layer chromatographic plate; on, in or from an electrophoresis gel, on or from an electroblotted membrane, or combinations thereof. In another embodiment, the sample holding means is any conventional single or multi-chambered containment article. The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 4-10)

85. The apparatus as in claim 50, wherein said analyte solution comprises: a matrix-free analyte solution.	Matrix refers to any solid or liquid molecules having an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof, and having an ability to transfer or receive a charge from the analyte. (page 11, lines 1-5) The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump. (page 13, lines 8-10)

Conclusion

Should the Examiner have any questions or comments, the undersigned can be reached at (949) 567-6700.

The Commissioner is authorized to charge any fee which may be required in connection with this Response to deposit account No. 50-1078.

Respectfully submitted,

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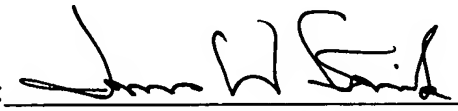
By: 

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